

Amendment to the Claims

Listing of the Claims

1. (Currently amended) A **trans-chromosomic** nonhuman **mammal comprising a cell** ~~mammalian~~ which harbors **a human chromosome fragment expressing** at least one human cytochrome P450 gene, ~~wherein the expression of the gene is induced by a compound serving as a substrate for a product of the gene.~~

2. (Currently amended) ~~[[A]]~~ **The trans-chromosomic** nonhuman **mammal** ~~mammalian~~ according to claim 1, wherein said human cytochrome P450 gene belongs to a CYP3A family.

3. (Currently amended) ~~[[A]]~~ **The trans-chromosomic** nonhuman **mammal** ~~mammalian~~ according to claim 1, wherein said human **chromosome fragment** ~~cytochrome P450 gene~~ is introduced by ~~introduction of a YAC vector containing the gene or microcell fusion using~~ **the** ~~[[a]]~~ chromosome fragment ~~containing the gene.~~

4. (Currently amended) **The trans-chromosomic** ~~[[A]]~~ nonhuman **mammal** ~~animal~~ according to claim 3, wherein the **mammal** ~~mammalian~~ is a chimeric **mammal** ~~animal~~.

5. (Currently amended) A nonhuman **mammal** ~~animal~~, which is obtained by mating a wild-type nonhuman **mammal** ~~animal~~ of the same kind as the nonhuman **mammal** ~~animal~~ according to claim 4 with the nonhuman **mammal** ~~animal~~ according to claim 4 and which harbors a **human** chromosome fragment containing a human cytochrome P450 gene.

6. (Withdrawn) A nonhuman mammalian according to claim 1, wherein a cytochrome P450 gene inherent to said nonhuman mammalian that is a homolog of said human cytochrome P450 gene has been disrupted and expression of the inherent gene has been reduced or lost.

7. (Canceled)

8. (Currently amended) ~~[[A]]~~ **The trans-chromosomic nonhuman mammal** ~~mammalian~~ according to claim 1, wherein the **mammal** ~~mammalian~~ is a mouse.

9. (Currently amended) A cell, ~~[[or]]~~ organ, or tissue **which is a cell of, or which comprises a cell** ~~containing the cell, the cell being~~ derived from, the **trans-chromosomic nonhuman mammal of mammalian** ~~according to claim 1~~ and **which is** capable of expressing a human cytochrome P450 gene.

10. (Withdrawn) A method for preparing a physical map for determining arrangement of mouse Cyp3a genes on a chromosome, comprising the steps of: (a) screening a mouse BAC library by PCR or hybridization using PCR primers or a probe for hybridization for specifically detecting each mouse Cyp3a genes; (b) repeating a cycle of screening the BAC library several times to prepare a BAC contig, the cycle comprising determining a terminal nucleotide sequence of the BAC clones selected in the above step and preparing a primer or a probe based on the nucleotide sequence; and (c) determining both ends of a Cyp3a gene cluster by preparing a full-length cDNA probe of an unprescribed mouse Cyp3a gene and performing hybridization of the above-mentioned BAC contig using the probe under the gentle conditions.

11. (Withdrawn) A physical map which can be prepared by the method according to claim 10 and having elucidated the arrangement of the mouse Cyp3a genes on the chromosome.

12. (Withdrawn) A method of preparing a targeting vector for deleting mouse Cyp3a genes, comprising cloning a genome DNA corresponding to respective terminals of a mouse Cyp3a gene cluster based on the physical map according to claim 11 and inserting each of the obtained cloned fragments into a vector containing a loxP sequence, which is a recognition sequence of recombinase Cre derived from bacteriophage P1.

13. (Withdrawn) A pair of targeting vectors for deleting mouse Cyp3a genes that can be prepared by the method according to claim 12, wherein the respective vectors are to be incorporated in a mouse chromosome and only when said enzyme Cre is present, homologous

recombination occurs between the loxP sequences, thereby deleting the whole Cyp3a gene cluster.

14. (Withdrawn) A method of deleting Cyp3a genes of a mouse cell, comprising the steps of introducing the vector according to claim 13 into a cell retaining pluripotency of a mouse and expressing enzyme Cre.

15. (Withdrawn) A mouse cell that can be prepared by the method according to claim 14, being deficient in Cyp3a genes and retaining pluripotency.

16. (Withdrawn) A method of preparing a knockout mouse deficient in Cyp3a genes, comprising the step of differentiating the mouse cell according to claim 15.

17. (Withdrawn) A chimeric mouse or a progeny thereof prepared by the method according to claim 16, being deficient in Cyp3a genes.

18. (Withdrawn) A mouse or a progeny thereof deficient in Cyp3a genes, obtained by mating the chimeric mouse according to claim 17 or a progeny thereof with a wild-type mouse.

19. (Withdrawn) A tissue derived from the chimeric mouse according to claim 16 or a progeny thereof or the chimeric mouse according to claim 17 or a progeny thereof.

20. (Withdrawn) A cell derived from the chimeric mouse according to claim 16 or a progeny thereof or the chimeric mouse according to claim 17 or a progeny thereof.

21. (Withdrawn) A mouse or a progeny thereof obtained by mating the mouse according to claim 8 or a progeny thereof with the chimeric mouse according to claim 17 or a progeny thereof, or the mouse according to claim 18 or a progeny thereof, the mouse or a progeny harboring a human chromosome containing human P450 genes and being deficient in mouse Cyp3a genes.

22. (Withdrawn) A method of producing biologically active human cytochrome P450, comprising the steps of cultivating an individual, tissue or cell of the mouse according

to claim 8 or a progeny thereof, expressing the human cytochrome P450 genes harbored therein to produce biologically active human cytochrome P450, and recovering the human cytochrome P450.

23. (Withdrawn) A method of producing biologically active human cytochrome P450, comprising the steps of cultivating an individual, tissue or cell of the mouse according to claim 21 or a progeny thereof, expressing the human cytochrome P450 genes harbored therein to produce biologically active human cytochrome P450, and recovering the human cytochrome P450.

24. (Withdrawn) A method of examining pharmacological effect and/or metabolism of a drug, comprising the step of administering the drug to an individual, tissue or cell of the mouse according to claim 8 or a progeny thereof or the mouse according to claim 21 or a progeny thereof.

25. (New) The trans-chromosomic nonhuman mammal according to claim 1, wherein the expression of the gene is induced by a compound which induces the expression of a human cytochrome P450 gene.